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An AC → ABC Approach to Taxol Involving B-Ring Closure at C-1–C-2

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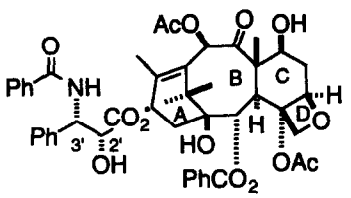
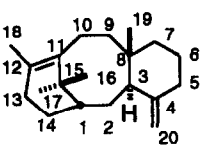
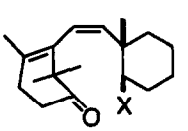
Abstract: The treatment of keto aldehyde **13** with low-valent Ti results in a stereoselective intramolecular pinacol coupling that produces taxane synthesis intermediate **14**.

Taxol[1] is currently one of the most compelling targets of total synthesis efforts.[2] These efforts are motivated by its challenging structure and clinically significant antitumor activity.[3] Previously, we disclosed a synthesis approach[2a] to the taxanes that involved A-ring annulation carried out on BC intermediates. Difficulty in modifying this route to incorporate C-ring functionality required by the natural taxanes forced us to consider alternative strategies. One that has received relatively little attention is the AC → ABC route that focuses on C-1–C-2 bond construction as the critical tricycle-forming step. Herein we outline the results of a feasibility study that demonstrates an intramolecular pinacol coupling to be effective in completing a tricyclic taxane structure through such a strategy.



TAXOL



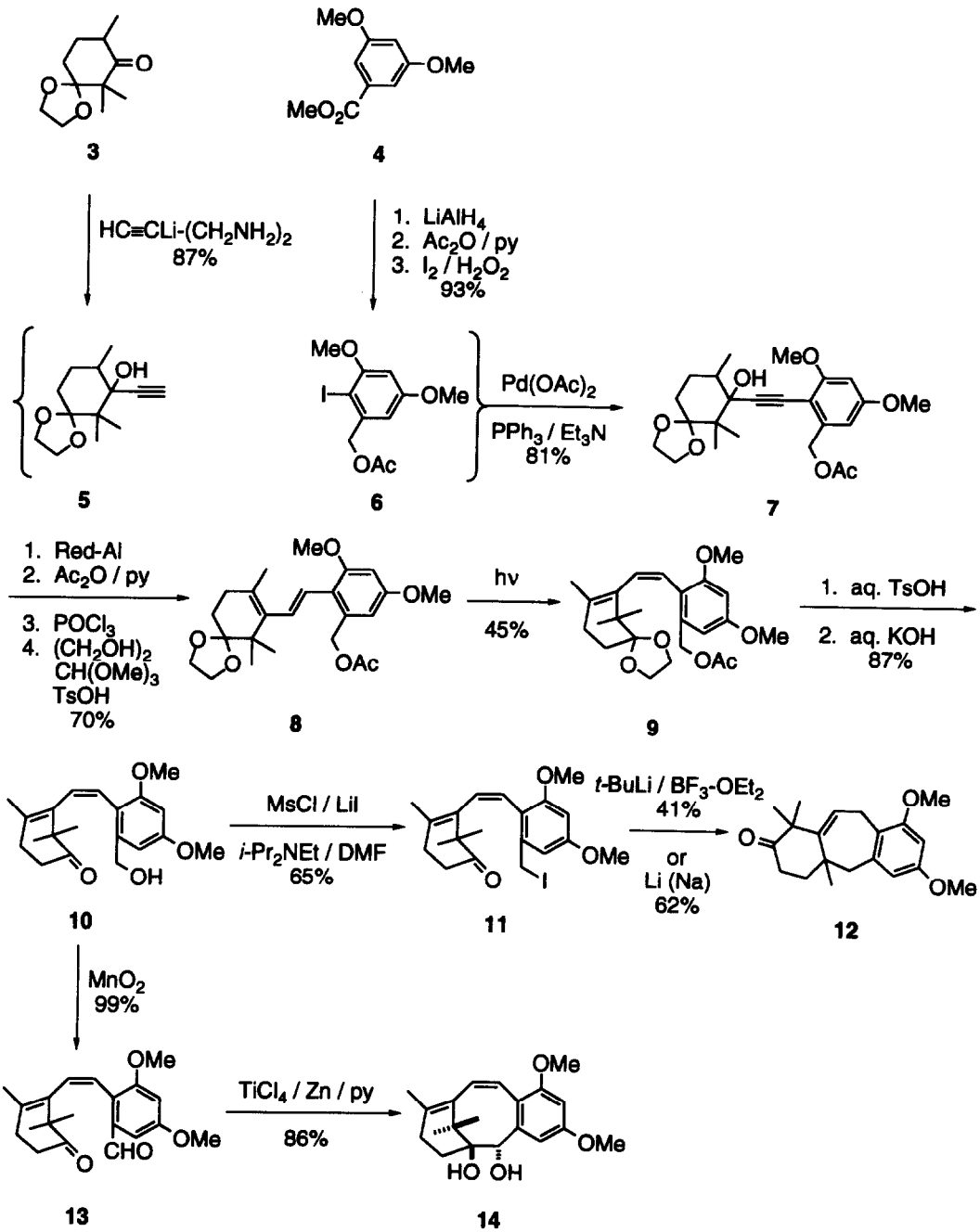


1 X = CH_2I

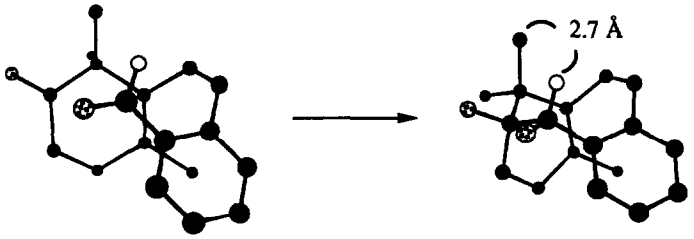
2 X = CHO

Preliminary work indicated the failure in our hands of Barbier or pinacol chemistry applied to saturated C-ring intermediates **1** and **2**, respectively, to provide for C-1–C-2 bond closure. We reasoned that the source of the difficulty was the intended annulation of the eight-membered B-ring onto the C-ring in *trans*-fused fashion, and decided to eliminate this feature by making the C-ring aromatic until after closure of the B-ring. The implementation of this plan is summarized in Scheme 1.

Monoketal **3**[4] could be converted to propargylic alcohol **5**, and the latter to arylated intermediate **7**.[5] After extensive failed attempts to effect the partial *cis* reduction of the acetylenic bond in **7** and related structures, **7** was converted to the corresponding *trans* allylic alcohol. Dehydration and re-establishment of the protection scheme gave **8**, which underwent photochemical isomerization to **9** with acceptable efficiency. Deprotection of **9** led to **10**.


MeO
OMe
MeO2C
3
4
HC≡CLi-(CH2NH2)2
87%
1. LiAlH4
2. Ac2O / py
3. I2 / H2O2
93%
OH
MeO
I
OMe
OAc
Pd(OAc)2
PPh3 / Et3N
81%
5
6
7
1. Red-Al
2. Ac2O / py
3. POCl3
4. (CH2OH)2
CH(OMe)3
TsOH
70%
hv
45%
1. aq. TsOH
2. aq. KOH
87%
8
9
MsCl / LiI
i-Pr2NEt / DMF
65%
t-BuLi / BF3-OEt2
41%
or
Li (Na)
62%
10
11
12
MnO2
99%
TiCl4 / Zn / py
86%
CHO
HO OH
13
14

Scheme 1



15 **16**

Scheme 2

Keto alcohol **10** was converted into iodide **11** to examine closure of the missing C-1–C-2 connection through the Barbier reaction. Both samarium (II)-mediated methods[6] and Zn-Cu couple gave complex mixtures from which meaningful products could not be isolated. On the other hand, the treatment of **11** with lithium-sodium dispersion proceeded cleanly, but to keto tricycle **12**. Interestingly, the same product was detected when **11** was treated with *t*-BuLi–BF_3-OEt_2.

Barbier chemistry having failed again, we turned to an examination of the pinacol closure. Intermediate **10** was converted into keto aldehyde **13**, which, upon treatment with low-valent titanium,[7] produced the desired tricyclic taxane structure **14** as a single diastereomer. We assign the relative stereochemistry of **14** from the observation of a nuclear Overhauser enhancement of the Me-16 proton singlet[8] when the H-2 singlet is saturated. The proximity of these groups (calculated[9] to be 2.7 Å in bis-desmethoxy model **16**; Scheme 2) can only arise in an endo conformation[10] when the C-2 proton is axial.[11]

The concomitant introduction in the conversion of **13** into **14** of oxygenation at C-1 and C-2 with appropriate relative stereochemistry is noteworthy. We speculate that the following factors are important: (1) the intervention of an endo transition structure;[12] (2) the preference of the C-2 oxygen for equatorial orientation; and (3) the reinforcement of this preference by the rotational bias of the formyl group. These features are indicated for the MM2 structures[9] of the bis-desmethoxy models of **13** and **14** in Scheme 2.

Whether it is **14** itself that develops into a viable taxane synthesis intermediate, or a close relative that might arise through similar pinacol chemistry remains to be seen. In any case, the efficient formation of **14** bodes well for the application of this strategy in a synthesis plan directed at taxol and related natural taxanes and taxol analogs.

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8. Data for **14**: ^{1}H NMR (300 MHz) δ 0.80 (s, 3H, Me-18), 1.14 (s, 3H, Me-17), 1.20 (s, 3H, Me-16), 1.59 (dt, 1H, J=3.3, 13.1, H-14), 2.17-2.31 (m, 3H, H-13, H-14), 2.93 (br s, 1H, OH), 3.28 (br s, 1H, OH), 3.78 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.74 (s, 1H, H-2), 6.33 (d, 1H, J=2.40, Ar H), 6.41 (app dd, 1H, J=1.21, 10.30, H-10), 6.52 (d, 1H, J=10.30, H-9), 6.88 (d, 1H, J=2.40, Ar H). Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.88; H, 7.83. For the methyl group assignments, see: Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953.
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